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EXAMINER	
BOWMAN, AMY HUDSON	
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1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,350	LEAKE ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *201-203,205-209,211,213,214,220,221,224-228 and 230-236* is/are pending in the application.

4a) Of the above claim(s) *203,205,208,209,211 and 214* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse in the reply filed on 7/10/08 is acknowledged. Applicant elected the species having the following modification scheme: a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end; the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification; the antisense strand has at least one phosphorothioate internucleotide linkage; a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand; and at least one conjugate cholesterol coupled to the 3' end of the sense strand.

In view of the foregoing election of species, Applicant believes that 201,202, 206, 207, 213, 220, 221, 224-227, 228, 230, 231,232, 233, 234, 235, and 236 read on the elected species.

Therefore, claims 203, 205, 208, 209, 211 and 214, as well as subject matter of claims that is not directed to the elected invention, is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/10/08.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c) or 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, none of the prior-filed applications disclose "active" and "inactive" strands of siRNAs, as recited in newly added claims 234-236 or disclose that the inactive strand 2'-O-alkyl modifications consist of modified nucleotides at the 5' end; or that the 5'-end consists of first and second nucleotides from the 5'-terminus having 2'-O-methyl modifications; or that the antisense region is "at least substantially complementary with the mRNA of the target gene".

Should applicant disagree, applicant is encouraged to point with particularity by page and line number to where such support exists. Therefore, the instant claims are accorded an effective filing date of 10/19/06, the filing date of the instant application.

Claim Objections

Claims 206 and 207 are objected to because of the following informalities: Claim 206 recites “wherein the antisense region includes at least one nucleotide other than first and second nucleotides having a 2' modification, wherein the 2' modification in the antisense region is selected from the group consisting of...". As currently drafted, it is unclear whether "having a 2' modification, wherein the 2' modification..." refers to the “at least one nucleotide" or the "first and second nucleotides”. For purposes of the instant search and corresponding examination, the claim is interpreted as reading, “wherein the antisense region includes at least one nucleotide that has a 2' modification selected from the group consisting of 2'-O-alkyl, 2'-deoxy, 2'-amine, 2'-alkyl, and 2'-fluoro, wherein the at least one nucleotide is not the first or second nucleotide of the antisense strand". Recitation of such would overcome this objection. Claim 207 is objected to because it depends from claim 206.

Appropriate correction is required.

Claims 228 and 230-233 are objected to because of the following informalities: It appears that applicant inadvertently omitted the word “and” after the last semi-colon in claim 228. Appropriate correction is required. Claims 230-233 are objected to because they depend from claim 228.

Claim 235 is objected to because of the following informalities: As currently drafted, claim 235 recites that the inactive sense strand 2'-O-alkyl modifications "consist of modified nucleotides at the 5' end". It is unclear what is meant by this phrase, as the 5' end has not been defined as referring to any specific number of nucleotides for the modifications to consist of. Appropriate correction and/or explanation is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 201 and 228 recite that that antisense region is "at least substantially complementary with the mRNA of the target gene". This limitation was first introduced into the claims filed on 11/10/06 and is not supported by the instant specification.

Claim 234 is directed to a siRNA comprising "an inactive sense strand" and an "active antisense strand". Claim 235 is directed to the siRNA of claim 234, wherein the

"inactive sense strand 2'-O-alkyl modifications consist of modified nucleotides at the 5' end". Claim 236 is directed to the siRNA of claim 234, wherein the "5' end consists of first and second nucleotides from the 5' terminus having 2'-O-methyl modifications".

However, the instant specification does not disclose "active" or "inactive" strands and does not define the strands or ends as recited in the instant claims.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

The claims are rejected for the reasons set forth above or for dependence upon one of the claims discussed above.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 11/10/06 and 12/5/07.

There is no support for these claim limitations in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 10/19/06, which is the filing date of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 201, 202, 206, 207, 213, 220, 221, 228, 230, 231, and 234-236 are rejected under 35 U.S.C. 102(b) as being anticipated by Giese et al. (US 2004/0180351 A1).

The instant claims are directed to a siRNA comprising a sense strand comprising a sense region, wherein the first and second nucleotides closest to the 5' end of the sense strand have a 2'-O-alkyl modification; and an antisense strand comprising an antisense region that is at least substantially complementary with the mRNA of the target gene and the sense region. Furthermore, a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end; the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification; the antisense strand has at least one phosphorothioate internucleotide

linkage; and a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

Giese et al. teach siRNA molecules comprising a sense and an antisense strand, comprising a sense region and an antisense region, respectively, wherein the antisense region is complementary with the mRNA of a target gene and is complementary with the sense region.

Giese et al. teach various combinations and patterns of modifications for siRNA duplexes. Giese et al. teach that the siRNAs can be blunt-ended or can comprise a 3'-overhang of at least one nucleotide on the sense or antisense strand. Giese et al. teach siRNA molecules fully modified with 2'-O-methyl modifications, as well as siRNA modification schematics with alternating 2'-O-methyl regions, wherein the 5' terminal nucleotides on the sense strand are modified (see Figure 2, for example). Giese et al. teach an siRNA, for example, that is fully modified with 2'-O-methyl modifications with 2 nt 3'-overhangs on the sense and antisense strands (TT) (see duplex 79A79B in Figure 8, for example).

Giese et al. teach that it is particularly advantageous to inactivate the sense strand of any of the RNAi forms of any of the embodiments, preferably via end modification, and more preferably a 5' end modification. Giese et al. teach that the advantage of this strategy arises from the inactivation of the sense strand which might otherwise interfere with an unrelated single-stranded RNA in the cell (see paragraphs [0103] and [0167]). Furthermore, Giese et al. teach that the 5' end of the antisense

strand preferably has a free OH and that the 5' end of the sense strand is modified to inactivate the strand (see paragraph [0103] and Table 1, embodiments 7 and 8).

Giese et al. teach that a 5'-phosphate on the antisense strand is required for siRNA function, suggesting that cells check the authenticity of siRNAs through a free 5' OH which can be phosphorylated and allow only such bona fide siRNAs to direct target RNA destruction (see paragraph [0119]).

Giese et al. teach that each of the design elements may be combined (see paragraphs [0112] and [0113], for example). Giese et al. teach that in addition to the various modifications or designs of the inventive RNAi molecules, further or additional modification of the nucleotides may include the use of a phosphorothioate backbone of the RNAi molecules which may be either complete or partial in order to inhibit endonuclease function (see paragraph [0170]).

Giese et al. teach that 2'-O-alkyl modifications stabilize RNAi molecules against degradation, but to a certain degree this is counterbalanced by the effect that 2'-alkyl modifications generally result in a reduced knockdown activity. Giese et al. teach that accordingly, the design of RNAi molecules has to balance stability against activity (see paragraph [0176]). Giese et al. teach that the most efficient molecules were modified at alternating positions of both strands.

Therefore, the instant claims are anticipated by Giese et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giese et al. (US 2004/0180351 A1), in view of Vargeese et al. (US 2004/0110296 A1).

The instant claims are directed to a siRNA comprising a sense strand comprising a sense region, wherein the first and second nucleotides closest to the 5' end of the sense strand have a 2'-O-alkyl modification; and an antisense strand comprising an antisense region that is at least substantially complementary with the mRNA of the target gene and the sense region. Furthermore, a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end; the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification; the antisense strand has at least one phosphorothioate internucleotide linkage; a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand; and a conjugate, more specifically a cholesterol conjugate.

Giese et al. teach siRNA molecules comprising a sense and an antisense strand, comprising a sense region and an antisense region, respectively, wherein the antisense region is complementary with the mRNA of a target gene and is complementary with the sense region.

Giese et al. teach various combinations and patterns of modifications for siRNA duplexes. Giese et al. teach that the siRNAs can be blunt-ended or can comprise a 3'-overhang of at least one nucleotide on the sense or antisense strand. Giese et al. teach siRNA molecules fully modified with 2'-O-methyl modifications, as well as siRNA modification schematics with alternating 2'-O-methyl regions, wherein the 5' terminal nucleotides on the sense strand are modified (see Figure 2, for example). Giese et al. teach an siRNA, for example, that is fully modified with 2'-O-methyl modifications with 2

nt 3'-overhangs on the sense and antisense strands (TT) (see duplex 79A79B in Figure 8, for example).

Giese et al. teach that it is particularly advantageous to inactivate the sense strand of any of the RNAi forms of any of the embodiments, preferably via end modification, and more preferably a 5' end modification. Giese et al. teach that the advantage of this strategy arises from the inactivation of the sense strand which might otherwise interfere with an unrelated single-stranded RNA in the cell (see paragraphs [0103] and [0167]). Furthermore, Giese et al. teach that the 5' end of the antisense strand preferably has a free OH and that the 5' end of the sense strand is modified to inactivate the strand (see paragraph [0103] and Table 1, embodiments 7 and 8).

Giese et al. teach that a 5'-phosphate on the antisense strand is required for siRNA function, suggesting that cells check the authenticity of siRNAs through a free 5' OH which can be phosphorylated and allow only such bona fide siRNAs to direct target RNA destruction (see paragraph [0119]).

Giese et al. teach that each of the design elements may be combined (see paragraphs [0112] and [0113], for example). Giese et al. teach that in addition to the various modifications or designs of the inventive RNAi molecules, further or additional modification of the nucleotides may include the use of a phosphorothioate backbone of the RNAi molecules which may be either complete or partial in order to inhibit endonuclease function (see paragraph [0170]).

Giese et al. teach that 2'-O-alkyl modifications stabilize RNAi molecules against degradation, but to a certain degree this is counterbalanced by the effect that 2'-alkyl

modifications generally result in a reduced knockdown activity. Giese et al. teach that accordingly, the design of RNAi molecules has to balance stability against activity (see paragraph [0176]). Giese et al. teach that the most efficient molecules were modified at alternating positions of both strands.

Giese et al. does not teach conjugates and therefore does not teach cholesterol conjugates.

Vargeese et al. teach conjugates including cholesterol, wherein the cholesterol conjugate is for the delivery of a siRNA molecule (see abstract and paragraph [0009], for example). Vargeese et al. teach that the conjugates are used to facilitate delivery of molecules into a biological system such as a cell. Vargeese et al. teach that the conjugates can impart therapeutic activity by transferring therapeutic compounds across cellular membranes (see paragraph [0009]).

It would have been obvious to incorporate a cholesterol conjugate into the siRNA molecules of Giese et al. and it would have been obvious to couple the conjugate molecule to the 3' end of the sense or antisense strand.

One would have been motivated to incorporate a cholesterol conjugate into the siRNA molecules of Giese et al. and would have been motivated to couple the conjugate molecule to the 3' end of the sense or antisense strand because Vargeese et al. teaches that cholesterol conjugates are used to facilitate delivery of molecules into a biological system such as a cell and can impart therapeutic activity by transferring therapeutic compounds such as siRNAs across cellular membranes. Since Vargeese et al. teach the advantage of conjugating nucleic acids including siRNAs to conjugates

such as cholesterol to enhance the delivery of the molecule; one would have been motivated to incorporate the conjugate into the siRNA of Giese et al. to enhance the delivery thereof. Furthermore, since Giese et al. teaches chemical modifications to enhance the stability of the siRNA molecule, one would have certainly been motivated to incorporate other means of enhancing the delivery of the molecule as well, such as cholesterol conjugation, as taught by Vargeese et al.

With regards to the cholesterol conjugate being coupled at the 3' end of the sense or antisense strand, this is considered an element of routine optimization to determine the optimal location within the duplexes of Giese et al. Moreover, Giese et al. teaches that necessity of a 5' phosphate on the antisense strand for active siRNA molecules, therefore one would have been motivated to incorporate the conjugate at the 3' end. Additionally, Vargeese et al. teaches configurations for coupling the conjugates which is within the realm of routine optimization.

It would have been prima facie obvious to perform routine optimization to determine optimal location for coupling the cholesterol conjugate of Vargeese et al., as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular administration ranges used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the

results should be considered unexpected in any way as compared to the closest prior art.

Finally, one of skill in the art would have had a reasonable expectation of success at incorporating a cholesterol conjugate into the siRNA molecules of Giese et al. and would have a reasonable expectation of success when coupling the conjugate molecule to the 3' end of the sense or antisense strand because Giese et al. teaches that a 5' phosphate on the antisense strand is necessary for activity and Vargeese et al. teaches the advantages of conjugating nucleic acids such as siRNAs to conjugates such as cholesterol. One would reasonably expect for a cholesterol conjugate to benefit the delivery of the siRNA molecules of Giese et al. given the teachings of Vargeese et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giese et al. (US 2004/0180351 A1), in view of Vargeese et al. (US 2004/0110296 A1), as explained in the rejection under 35 USC 103(a) above, further in view of Fire et al. (US 6,506,559 B1).

It is noted that the instant claims are directed to siRNA comprising sense and antisense strands that do not have any size limitation and thus read on longer dsRNA

molecules. Furthermore, the instant specification does not define siRNA molecules to exclude longer duplexes. Recitation of "consisting" of language or recitation of an upper limit of the length of the siRNA molecule that is supported by the specification, for example, would obviate this rejection.

Fire et al. teaches a method of inhibiting the expression of a target gene in a cell comprising introduction of a double-stranded RNA molecule in an amount sufficient to inhibit the expression of the target gene, wherein the double-stranded RNA has a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene (see claim 1). Fire et al. teaches that the double-stranded RNA can be directly injected into the cell or extracellularly injected into the organism (see column 5). Fire et al. teach that the method may be used to introduce RNA into a cell for the treatment of a disease (see column 9) and that the invention is not limited to any type of target gene or nucleotide sequence (see column 11). Fire et al. exemplifies the method of dsRNA inhibition in *C.elegans* via RNA interference (see column 14). Fire et al. teaches that higher doses of the dsRNA resulted in more effective inhibition. Fire et al. teach that lipid-mediated carrier transport or chemical-mediated transport can be used to deliver the RNA molecules (see column 9). Fire et al. teach that double-stranded RNA-mediated inhibition has advantages both in the stability of the material to be delivered and the concentration required for effective inhibition (see column 3).

Fire et al. teaches a method of inhibiting the expression of a target gene in a cell comprising introduction of a double-stranded RNA molecule in an amount sufficient to inhibit the expression of the target gene, wherein the double-stranded RNA has a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene (see claim 1). Fire et al. teaches that the double-stranded RNA can be directly injected into the cell or extracellularly injected into the organism (see column 5). Fire et al. teach that the method may be used to introduce RNA into a cell for the treatment of a disease (see column 9) and that the invention is not limited to any type of target gene or nucleotide sequence (see column 11). Fire et al. exemplifies the method of dsRNA inhibition in *C. elegans* via RNA interference (see column 14). Fire et al. teaches that higher doses of the dsRNA resulted in more effective inhibition. Fire et al. teach that lipid-mediated carrier transport or chemical-mediated transport can be used to deliver the RNA molecules (see column 9). Fire et al. teach that double-stranded RNA-mediated inhibition has advantages both in the stability of the material to be delivered and the concentration required for effective inhibition (see column 3).

It would have been obvious to incorporate the modifications of Giese et al. and Vargeese et al. into a longer dsRNA, as taught by Fire et al. because Fire et al. teaches the benefits of such molecules that act via RNAi. Furthermore, Fire et al. teaches that dsRNA molecules are utilized in methods of inhibiting target gene expression and treating diseases via RNA interference. Armed with the knowledge of Fire et al., one

would be motivated to utilize the method of Fire et al. to design a dsRNA with the modifications of Giese et al. and Vargeese et al. to enhance the stability and delivery of the dsRNA molecules.

Since Fire et al. teach that double-stranded RNA-mediated inhibition has advantages both in the stability of the material to be delivered and the concentration required for effective inhibition, one would have been motivated to utilize a dsRNA.

Since Fire et al. teaches a method of inhibiting target gene expression with dsRNA molecules and teaches the benefits of these molecules to other antisense approaches, one would have had a reasonable expectation of success in utilizing the long dsRNA molecules of Fire et al. to achieve RNAi silencing of a target and one would expect for the modifications of Giese et al. and Vargeese et al. to add the benefits of stability and enhanced delivery of the dsRNA molecules of Fire et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 201 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, and 7 of copending Application No. 11/825,461. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of application '461 is directed to using siRNA molecules that are modified with 2'-O-methyl modifications at positions 1 and 2 of the sense region, which are structural characteristics of the instant siRNA molecules. Therefore, the instant compounds and the method of application '461 are obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 201, 202, 206, 207, 213, 220, 221, 224-228, and 230-236 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33 of copending Application No. 11/619,993. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of application '993 is directed to using siRNA molecules

that have identical structural characteristics including modification requirements, phosphate requirements, and conjugate requirements to the instant siRNA molecules. Therefore, the instant compounds and the method of application '993 are obvious in view of each other. Furthermore, the specification of application '993 defines the siRNA molecules as being blunt ended or comprising overhangs.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that there is not a restriction requirement between the instant compounds and the methods of applications ‘461 and ‘993.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Examiner
Art Unit 1635

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